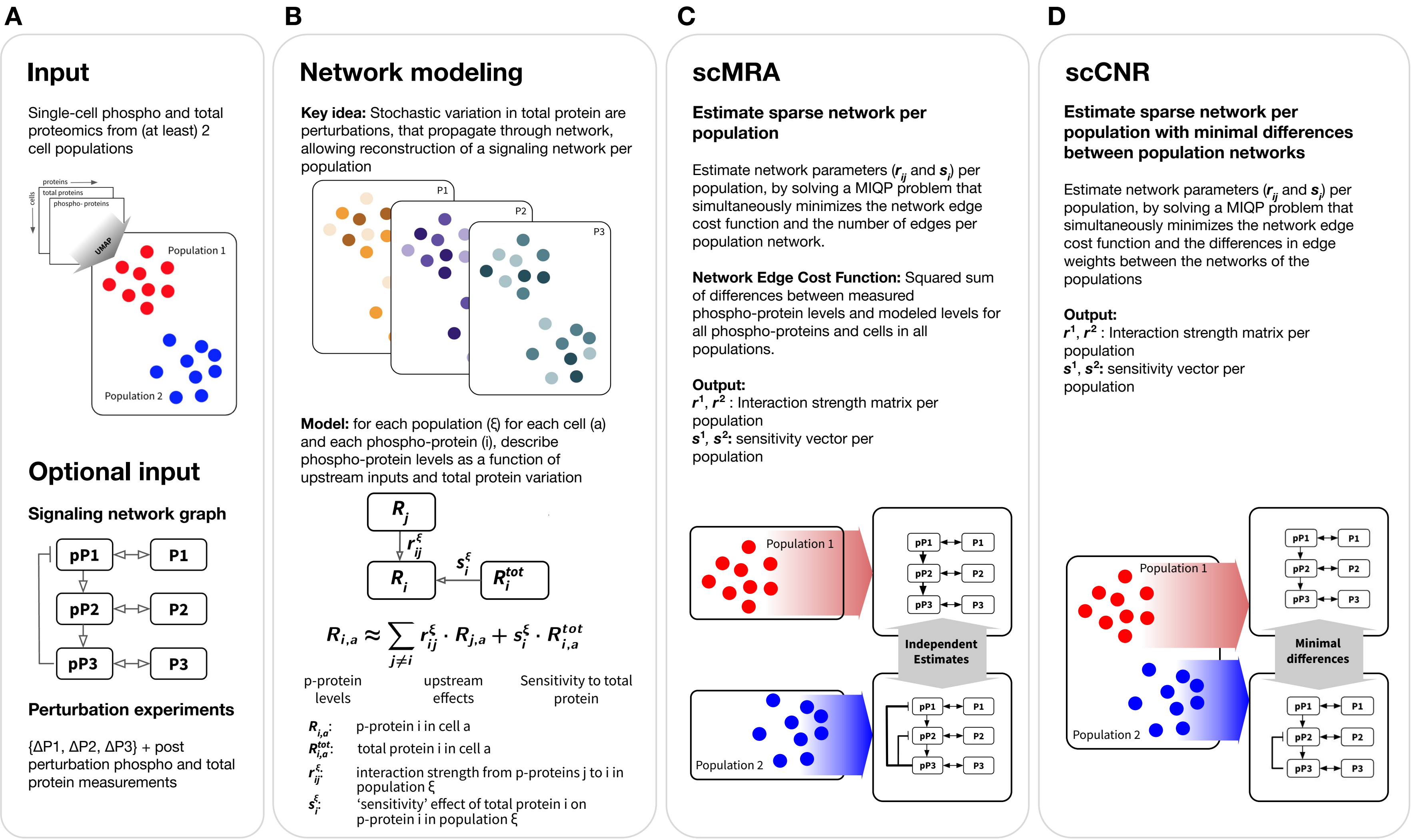

A
Input
Single-cell phospho and total proteomics from (at least) 2 cell populations
proteins
total proteins
phospho- proteins
cells
UMAP
Population 1
Population 2
Optional input
Signaling network graph
pP1
P1
pP2
P2
pP3
P3
Perturbation experiments
{ΔP1, ΔP2, ΔP3} + post perturbation phospho and total protein measurements
B
Network modeling
Key idea: Stochastic variation in total protein are perturbations, that propagate through network, allowing reconstruction of a signaling network per population
P1
P2
P3
Model: for each population (ξ) for each cell (a) and each phospho-protein (i), describe phospho-protein levels as a function of upstream inputs and total protein variation
R_j
r_{ij}^{ξ}
R_i
s_i^{ξ}
R_i^{tot}
$R_{i,a} \approx \sum_{j \neq i} r_{ij}^{\xi} \cdot R_{j,a} + s_i^{\xi} \cdot R_{i,a}^{tot}$
p-protein levels
upstream effects
Sensitivity to total protein
$R_{i,a}$: p-protein i in cell a
$R_{i,a}^{tot}$: total protein i in cell a
r_{ij}^{ξ}: interaction strength from p-proteins j to i in population ξ
s_i^{ξ}: 'sensitivity' effect of total protein i on p-protein i in population ξ
C
scMRA
Estimate sparse network per population
Estimate network parameters (r_{ij} and s_i) per population, by solving a MIQP problem that simultaneously minimizes the network edge cost function and the number of edges per population network.
Network Edge Cost Function: Squared sum of differences between measured phospho-protein levels and modeled levels for all phospho-proteins and cells in all populations.
Output:
r^1, r^2 : Interaction strength matrix per population
s^1, s^2: sensitivity vector per population
Population 1
Population 2
pP1
P1
pP2
P2
pP3
P3
Independent Estimates
D
scCNR
Estimate sparse network per population with minimal differences between population networks
Estimate network parameters (r_{ij} and s_i) per population, by solving a MIQP problem that simultaneously minimizes the network edge cost function and the differences in edge weights between the networks of the populations
Output:
r^1, r^2 : Interaction strength matrix per population
s^1, s^2: sensitivity vector per population
Population 1
Population 2
pP1
P1
pP2
P2
pP3
P3
Minimal differences